REMARKS

Examination of claims 1-3, 5, and 13-43 is reported in the present Office Action. Claims 1-3, 5, 13, 15, 16, 18, and 23 were rejected under 35 U.S.C. § 102(b), and claims 14, 17, 19-22, and 24-43 were rejected under 35 U.S.C. § 103(a). Each of the rejection is addressed as follows.

First, Applicants note that claims 1, 15, and 16 have been amended to specify that the treated patients are in need of the induction of insulin sensitizing or insulin mimetic effects. Applicants further note the addition of new claims 44 to 46, which specifies a method for inducing an insulin sensitizing or insulin mimetic effect in a tissue of a patient having hyperinsulinemia and methods to combat insulin resistance or to combat hyperinsulinemia in a patient in need thereof. Support for these amendments can be found throughout the application, for example, at page 4, lines 13-17. No new matter is added by the amendments.

Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 5, 13, 15, 16, 18, and 23 were rejected under 35 U.S.C. § 102(b) as being anticipated by Sauvaire et al., U.S. Patent No. 5,470,879. Applicants respectfully request that this rejection be withdrawn for the following reasons.

This rejection is based on the Examiner's assertions that the present claims specify a method of treating type II diabetes by administration of 4-hydroxyisoleucine and/or the lactonic form thereof, and that Sauvaire teaches the same method. With respect to Applicants' specification of inducing an insulin sensitizing or insulin mimetic effect in the present claims, the Examiner states that this "is merely a property or function of the formula." Applicants respectfully disagree.

In this rejection, the Examiner cites *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1947 (Fed. Cir. 1999), for teaching that "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning does not render the old composition patentably new to the discoverer." In response, Applicants note that they are not attempting to claim an old composition. Rather, as discussed below, Applicants are claiming new methods, based on their discovery of new properties of a composition that was previously known for use for a different purpose. The law makes it clear that such new methods are patentable. (See, e.g., *In re Marshall*, 578 F.2d 301 (C.C.P.A. 1987); *In re Shetty* 566 F.2d 81 (C.C.P.A. 1977); *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001); *Perricone v. Medicis Pharmaceutical Corporation*, 432 F.3d 1368 (Fed. Cir. 2005)).

Turning now to the specifics of this case, Applicants submit that stimulation of insulin secretion (as taught by Sauvaire) and insulin sensitization (as in the present invention) are two different processes, taking place in completely different cell types. Some drugs such as sulfonylureas possess secretagogue activity (i.e., stimulate insulin secretion), but do not stimulate glucose uptake (i.e., increase insulin sensitization), whereas other drugs such as metformin can stimulate glucose uptake but have no effect on insulin levels. Other drugs such as GLP-1 analogues have both activities. Thus, as not all drugs acting through one of the two processes described above (insulin secretion and insulin sensitization) necessarily act through the other, it cannot be assumed that a compound such as 4-hydroxyisoleucine, which was known to be capable of stimulating insulin secretion (as shown by Sauvaire), will automatically have an insulin sensitizing or insulin mimetic effect, as in the present invention.

Applicants' specification of inducing an insulin sensitizing or insulin mimetic effect is

therefore not "merely a property or function of the formula." Rather, this specification delineates particular patient populations to be treated according to the methods of the present invention, in contrast to the methods of Sauvaire. In particular, the methods of the present invention provide treatment options for patients for whom treatment regimens based on the stimulation of insulin secretion would not have been considered. As an example, those skilled in the art, in view of Sauvaire's teaching that 4-hydroxyisoleucine stimulates insulin secretion, would certainly not have considered it helpful to treat patients who produce insulin at or near normal levels, but whose target tissues are not insulin responsive. In contrast, these patients could be treated according to the present invention, to obtain beneficial effects on their conditions, as the treatment would potentiate the insulin sensitizing and insulin mimetic effects of insulin already produced by the patient. The treatment of such patients is clearly specified in the present claims, which state that the methods are for treating patients in need of the induction of insulin sensitization or mimetic effects. The invention thus provides a novel approach to treating patients with conditions associated with abnormal glucose metabolism diabetes. Applicants therefore respectfully request that this rejection against claims 1-3, 5, 13, 15, 16, 18, and 23 be withdrawn.

Applicants further submit that the teaching of Sauvaire of administering 4-hydroxyisoleucine for the treatment of type II diabetes also does not inherently anticipate the present claims, for the following reasons. As is noted above, the present claims are drawn to methods of inducing insulin sensitizing or insulin mimetic effects in the tissues of patients in need thereof. These effects are beneficial to patients who are insulin resistant, which means that their tissues that should respond to the effects of insulin (e.g., muscle, liver, and fat tissues) do

not do so. Treatment according to the methods of the invention results in increased sensitivity of tissues to insulin and/or results in an insulin mimetic effect.

As is provided in the M.P.E.P., in order for the prior art to support inherent anticipation, an "allegedly inherent characteristic must necessarily flow from the teachings of the applied prior art" (M.P.E.P. 2112 (IV); citations omitted). The M.P.E.P. further states on this matter that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" (M.P.E.P. 2112 (IV); citations omitted; emphasis in original). In addition, this section of the M.P.E.P. provides that "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient" (M.P.E.P. 2112 (IV); citations omitted). These passages makes it clear that, for Sauvaire to inherently anticipate the present claims, Sauvaire must describe a method that necessarily results in the effects of the methods of the present claims: insulin sensitizing or insulin mimetic effects in patients in need thereof. As is discussed below, this is not the case.

Although many patients having type II diabetes have insulin resistance, and thus could benefit by the induction of insulin sensitizing or insulin mimetic effects, this is not the case for all type II diabetes patients. For example, Haffner et al. (Diabetes 46:63-69, 1997) report that the percentage of insulin-sensitive type II diabetics ranges between 4.9-14.3% in different ethnic populations (see page 65, Table 1).

In another example, Campbell et al. (Metabolism 37:15-21, 1988) report that, in a study of type II diabetics with body mass indices of < 30 kg/m^2, a large percentage of the subjects are insulin-sensitive:

> [I]n the present study almost one third of our NIDDM subjects had no evidence of either hepatic or peripheral insulin resistance. In these subjects, reduced insulin-resistance must have been the factor responsible for hyperglycemia. Thus, our results indicate that NIDDM is a heterogeneous disorder and that impaired insulin secretion need not invariably be associated with insulin resistance. (Page 20, right column, second paragraph.) (Emphasis added.)

In a further example, Banerji et al. (Diabetes 44:141-146, 1996) state:

> Insulin resistance in black Americans with non-insulin-dependent diabetes mellitus (NIDDM) is found in only 60% of those with a body mass index (BMI) of <30 kg/m^2, suggesting that NIDDM can occur independent of peripheral insulin resistance. (Page 141, Abstract.) (Emphasis added.)

Further support for a sub-population of insulin-sensitive type II diabetics is provided by Arner et al. (Diabetologia 34:483-487, 1991) and Nesher et al. (Eur. J. Clin. Invest. 17:266-274, 1987). Arner et al. report that all their non-obese diabetic subjects "had insulin secretory values far below the normal range and all the M/I values were evenly distributed within the normal range;" wherein, M/I represents insulin sensitivity index (see page 485, right column, first paragraph, and Figure 1). Nesher et al. described similar results:

> Obese Type 2 DM [diabetes mellitus] were as resistant to insulin as non-diabetic obese controls, while lean diabetic patients showed no evidence of insulin resistance, whether low or high doses of insulin were used. Indeed, the PSS [Peripheral Insulin Sensitivity Score] values of the diabetics were higher than normal, suggesting increased sensitivity to insulin in our patients. (Page 272, left column, second paragraph.) (Emphasis added.)

Thus, type II diabetes is a heterogeneous disease, and includes individuals that are insulin sensitive and other individuals that are insulin resistant. Therefore, treatment of type II diabetes, according to the method of Sauvaire, does not necessarily result in the induction of an insulin sensitizing or insulin mimetic effect in patients in need thereof, according to the methods of the

present invention. The teachings of Sauvaire, therefore, do not inherently anticipate the present claims.

A rejection of new claims 44 to 46 should not be made over the Sauvaire reference. As is noted above, these claims specify that the claimed methods are for combating insulin resistance or combating hyperinsulinemia. As is known in the art, insulin resistance and hyperinsulinemia are conditions that are characterized by excess insulin in the blood (see, e.g., the enclosed definition of hyperinsulinemia from Stedman's Medical Dictionary). Hyperinsulinemia and insulin resistance occur in patients that are resistant to the action of insulin at its target tissues (e.g., muscle and liver). Treatment of those conditions thus may be focused on increasing insulin sensitivity of such target tissues, and it is such an approach that is the subject of the present invention.

As is discussed above, a central teaching of the Sauvaire patent is the activity of 4-hydroxyisoleucine on stimulating insulin secretion. For example, in contrasting their findings with the prior art, Sauvaire states "the specialists have consequently been led quite naturally to look for products capable of stimulating insulin secretion; among these, only sulfonamides (sulfonylureas) have evinced efficacy..." (column 1, lines 37-42). After making note of drawbacks of sulfonylureas, Sauvaire goes on to state "it would consequently be desirable to be able to have available a medicinal product that can act as a substitute for sulfonylureas for stimulating insulin secretion while not possessing the abovementioned drawbacks... This was the objective which was set according to the invention." (column 1, lines 52-57).

In another example showing that the teachings of Sauvaire are based on the stimulation of insulin secretion, Sauvaire states "[t]he invention relates especially to a composition endowed

with insulin-stimulating properties..." (column 3, lines 3-6). In addition, the experimental examples of Sauvaire focus on increasing insulin secretion from pancreatic islet cells (Example 2) and isolated pancreas (Example 3). The *in vivo* studies of Sauvaire make note of the induction of hyperinsulinemia, as a result of the administration of 4-hydroxyisoleucine. For example, in Example 4, Sauvaire states "this table shows that administration of 4-hydroxyisoleucine triggers an immediate and particularly important increase in the plasma insulin level" (column 6, lines 6-9), while in Example 5, Sauvaire states "...4-hydroxyisoleucine triggers a very rapid and considerable rise in blood insulin level..." (column 6, lines 45-47).

Thus, it is clear that the teachings of Sauvaire are based on the stimulation of insulin secretion. Indeed, Sauvaire teaches that the induction of hyperinsulinemia is beneficial to the claimed treatment. Patients treated according to the method of Sauvaire would therefore not be patients having hyperinsulinemia or insulin resistance, as specified in claims 44 to 46. Thus, similar to the other claims in this case, Sauvaire does not anticipate claims 44 to 46, as different patients are treated according to the methods of Sauvaire (patients requiring increased insulin levels) and those of the claims 44 to 46 (patients having excess insulin levels). In view of the above, Applicants submit that a rejection of claims 44 to 46 over Sauvaire not be made.

Rejection under 35 U.S.C. § 103(a)

Claims 19-22 and 24-43 were rejected under 35 U.S.C. § 103(a) for obviousness over Sauvaire et al., U.S. Patent No. 5,470,879, in view of Guittard, U.S. Patent No. 5,178,867. Applicants respectfully request that this rejection be withdrawn.

Sauvaire is cited for teaching the administration of 4-hydroxyisoleucine for the treatment

of type II diabetes, as discussed above. The Examiner states that Sauvaire does not teach administration of 4-hydroxyisoleucine twice or three times per day (claims 19, 20, 28, 29, 38, and 39), or that the form of 4-hydroxyisoleucine is a capsule or a tablet (claims 21, 22, 30, 31, 40, and 41), however states that such uses would be obvious, in light of Sauvaire's statements that excipients are chosen in accordance with the pharmaceutical dosage form adopted and dosages can vary within wide limits. Guittard is cited for teaching that tablets and capsules are a convenient and economical form of drug administration for oral ingestion.

As is discussed in detail above, with respect to the rejection under 35 U.S.C. § 102(b), the present claims specify the induction of an insulin sensitizing or insulin mimetic effect in patients in need of such effects, which is not taught or suggested by Sauvaire. Indeed, the effects desired according to the teachings of Sauvaire (increased insulin secretion) and the present invention (treatment of excess insulin levels) are different. Thus, regardless of knowledge as to variation of dosages or the teachings of Guittard with respect to the form of drug administration, Applicants submit that the cited references do not provide any suggestion or motivation to induce the effects of the present invention. The present invention is therefore non-obvious over the prior art and, thus, this rejection should be withdrawn.

Claims 14 and 17 were rejected under 35 U.S.C. § 103(a) for obviousness over Sauvaire et al., U.S. Patent No. 5,470,879, in view of Davydov, U.S. Patent No. 4,529,589. Applicants respectfully request that this rejection be withdrawn.

Sauvaire is cited for teaching administration of 4-hydroxyisoleucine for the treatment of type II diabetes, while Davydov is cited for teaching that insulin is well-known in the art as being used for the treatment of diabetes mellitus. Quoting *In re Kirkhoven*, 205 U.S.P.Q. 1069, CCPA

1980, the Examiner states "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose..."

In response, Applicants note that it would not have been obvious to use 4-hydroxyisoleucine for the purpose of the present claims, inducing of insulin sensitizing or mimetic effects, as discussed above. Prior to the present invention, these effects of 4-hydroxyisoleucine simply were not known, and the use of 4-hydroxyisoleucine as now claimed is not inherent in the teachings of the prior art, because, as discussed above, the present methods provide for the treatment of patients who would not have been considered for treatment by the methods of Sauvaire. The teachings of Davydov that insulin is a well-known treatment for diabetes mellitus does not impact the deficiencies of Sauvaire in supporting this rejection. Prior to the present invention there were no teachings or suggestions in the art to administer amino acids such as 4-hydroxyisoleucine to patients in need of the induction of insulin sensitizing or mimetic effects, as now claimed, and, therefore, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 5, 2007

Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045